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The economic burden of caregiving on families of children and adolescents with cancer:**A population-based assessment**

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Abstract

Background: Childhood cancer represents a relevant economic burden on families. The preferred tool to investigate family expenditure is the retrospective questionnaire, which is subject to recall errors and selection bias. Therefore, in the present study the economic burden of caregiving on families of children and adolescents (0-19 years of age) with cancer was analysed using administrative data as an alternative to retrospective questionnaires.

Procedure: Incident cases of cancer diagnosed in children and adolescents in 2000-2005 (N=917) were identified from the Piedmont Childhood Cancer Registry and linked to available administrative databases to identify episodes of care during the 3 years after diagnosis (N=13,433). The opportunity cost of informal caregiving was estimated as the value of the time spent by one of the parents, and was assumed to be equal to the number of days during which the child received inpatient care, day-care, or outpatient radiotherapy. Factors affecting the level of economic burden of caregiving on families were analysed in a multivariable model.

Results: The economic burden of caregiving increased when care was supplied at the Regional Referral Centre, or when treatment complexity was high. Families with younger children had a higher level of economic burden of caregiving. Leukaemia required a higher family commitment than any other cancer considered.

Conclusions: Raw estimates of the economic burden of caregiving on families of children and adolescents with cancer derived from administrative data should be considered a minimum burden. The estimated effect of the covariates is informative for healthcare decision-makers in planning support programmes.

Introduction

Household out-of-pocket health expenditure comprises all costs paid directly by patients or their relatives, including cost-sharing, self-medication and other expenditures. Even in a publicly financed health care system, users are faced with expenses due to transportation, out-of-pocket costs and the cost of time spent caring for patients with the disease, or being with the patient while care is received (foregone income) [1]. In the case of childhood diseases, the time parents (especially mothers) have to take away from work and other activities to care for their children represents a relevant economic burden. The economic burden of cancer treatment has long been described as a major source of anxiety for the families of paediatric cancer patients [2-4]. Mothers caring for children with cancer found it difficult to manage their daily family routines, and fathers found it difficult to manage work outside the home [5]. A study from the United Kingdom observed that 34.7% of working mothers gave up all paid employment when their children were diagnosed, and another 28.7% reduced their working hours [6]. In economics, the value of this time is referred to as the “opportunity cost” of informal caregiving [7]. Despite the recognised relevance of informal caregiving, one of the main limitations mentioned in a systematic review of the literature on the cost of childhood cancer [8] was the exclusion of indirect costs (e.g., loss of productivity, forgone household activities, unpaid caregiving and interrupted education due to illness and child’s premature mortality) and psychosocial costs.

Centralisation of care for children and adolescents with cancer has contributed to the very significant improvement in outcome seen over the past 30 years [9]. Depending on place of residence, travel may be unavoidable to access specialised centres that offer safe and effective services not available locally. This travel can range from daily trips, to long periods spent away from home, and the corresponding economic burden falls upon the family, with a high impact on out-of-pocket expenses and lifestyle [10,11].

The preferred tool to investigate patient/family expenditures is the retrospective questionnaire, which is subject to recall errors and selection bias, or in prospective studies, a diary into which entries are made over a specific time period. Even if the diary method comes with a risk of lower compliance, as data is collected over a long period of time, this method has been successfully adopted in cost-effectiveness studies [12]. However, for the parents of children with cancer the diary method could present a further burden, and cause psychological distress. In addition, compliance regarding diary entries is likely to be affected by children's health, with a consequent risk of selection bias.

This study attempts to verify the availability of alternative data sources for describing and understanding the economic burden of caregiving on families of children with cancer. This burden was assessed through cancer registry and administrative health data by means of several simplified assumptions. Administrative data are considered an important and efficient source of valuable information when assessing patterns of care, and their validity and usefulness have been previously demonstrated for cancer care in several studies carried out in the Piedmont Region [13-15]. Moreover, administrative data allow for a population-based analysis without the direct involvement of families.

The Childhood Cancer Registry of Piedmont (CCRP) was established 40 years ago. It is a population-based registry that records cases of malignant tumours diagnosed in children and adolescents (0-19 years of age) residing in the Piedmont Region. The procedures and criteria for inclusion in the CCRP, and follow-up and coding for cancer types have been reported elsewhere [16]. Through linkage between the CCRP and different administrative health databases, we have attempted to measure the opportunity cost of caring for children and adolescents with cancer during treatment episodes, thereby avoiding selection bias and the direct involvement of families. Factors impacting the level of economic burden of caregiving were investigated to better target activities that might support families.

Methods

Study data

Incident cases of cancer diagnosed in children and adolescents (0-19 years of age) residing in the Piedmont Region during the period 2000-2005 were identified from the CCRP (N=917). If multiple primary tumours were identified, only the first occurrence was taken into account in the analyses. For each child or adolescent, episodes of care (defined as inpatient care, day-care, or outpatient radiotherapy) were identified during the 3 years following the primary cancer diagnosis by means of an encrypted unique identification code based on the tax identification number within the Piedmont Region's hospital discharge records and outpatient radiation therapy databases (years 2000-2007). Both of these databases include episodes of care received by residents of the Piedmont Region, whether care was received in the Piedmont Region, or elsewhere in Italy. All episodes of care during the follow-up period, regardless of whether they were cancer-related, were included in the analyses, as was inpatient care with a discharge date that was 40 days or less before diagnosis.

Tumour types were classified according to the International Childhood Cancer Classification [17]. To achieve a better trade-off between number/levels of predictors and overall sample size, we grouped cancer types into wider categories by numerical considerations and prognoses, as defined by 3-year survival (Table I): cancer types with a 3-year survival above 85% (Hodgkin Disease, Wilms Tumour, Retinoblastoma, Gonadic Tumour, and all other tumours); cancer types with a 3-year survival between 75% and 85% (Non-Hodgkin lymphoma, Central Nervous System, Neuroblastoma); cancer types with a 3-year survival below 75% (Malignant Bone Tumours and Soft Tissue Sarcoma); and Leukaemia, which was set apart due to its high frequency (N=200) and good 3-year survival. Information available for each patient included: gender, age at diagnosis, cancer type, year of diagnosis, place of residence and 3-year survival. Travel time was categorised as the distance

from the patient's place of residence to Turin, where the Regional Referral Centre (RRC) for Childhood Cancer is located (same town, within 30 minutes, within 1 hour, more than 1 hour). A quadratic matrix of the travel time between all the towns of the Piedmont Region was used [18].

Each episode of day-care requires at least half a day, and can include several days of treatment. Each outpatient radiotherapy episode includes treatment planning, computed tomography scans, use of simulator, other procedural phases and treatment sessions. Episodes of care were classified according to the clinical setting (inpatient care, day-care, or outpatient radiotherapy) and the type of treatment (transplant, major and minor surgery, radiotherapy, chemotherapy and other medical care). All the surgical procedures performed were listed in the hospital discharge records for this cohort. A childhood cancer specialist working at the RRC reviewed these procedures and identified major surgery by means of the International Classification of Disease, 9th Revision (ICD9) codes. Chemotherapy, radiotherapy, major surgery and transplant were categorised as high complexity episodes of care according to a Regional Plan for Paediatric Oncology and Haematology Care [19].

In the analysis, the hospitals/centres that supplied care were classified by type as follows: the RRC, Satellite Units, Adult oncology centres, other hospitals in the Piedmont Region, and hospitals outside the Piedmont Region. According to the organisation of the Regional Network for Childhood Cancer Care, made up of the RRC and the Satellite Units, most of the care for childhood cancer should be supplied by either the RRC or the eight Satellite Units, which provide low complexity care in strict collaboration with the RRC. Adult oncology centres are also potential suppliers of appropriate cancer care for children and adolescents, especially those 14 years of age or older. The organisation of the Regional Network for Childhood Cancer Care states that no cancer care should be provided to children or adolescents by the other hospitals in the Piedmont Region. Anyway, some episode of care

were supplied by this group of hospitals. The final group consisted of hospitals in other regions of Italy, which were national referral centres for childhood/adolescents cancer care.

The economic burden of caregiving on families of children with cancer was assessed from a societal point of view [20], by valuing the opportunity cost associated with informal caregiving by one of the parents. Opportunity cost is often estimated by multiplying the hours spent providing informal care by the market wage rate of the informal caregiver. We referred to this method to estimate the yearly economic burden of caring for children during treatments based on a number of assumptions. The amount of time spent caregiving by one of the parents was assumed to be equal to the total number of days during which inpatient care, day-care, or outpatient radiotherapy were provided to the child/adolescent. As we did not have information on the parents' wage rate, the per diem Regional Gross Domestic Product (GDP) in 2008 (€78.60; US\$106.05) was applied for each day devoted to caring for the child or adolescent [21]. To assess robustness of the results obtained using these assumptions, a sensitivity analysis was performed using two different scenarios. One more conservative scenario was considered, which assumed a family commitment of half a day for episodes of day-care, outpatient care and inpatient admissions in children more than 14 years of age (minimum scenario). A second, less conservative scenario assumed 1 extra day after every episode of day-care and outpatient care, and 1 week after inpatient admissions for high complexity episodes of care.

Statistical analysis

The cumulative per-family 3-year economic burden of caring for the child or adolescent during treatment was described as median costs with corresponding 95% confidence intervals (CI), by accounting for censoring due to death by means of a Kaplan-Meier estimate. Factors affecting the level of economic burden were analysed in a multivariable model. Due to

collinearity with the type of centre, treatment complexity and travel time were not included in the final model.

As suggested by previous findings [22], the total cost at the end of follow-up was treated as a time-to-event endpoint, to which a Cox-Aalen model was fitted [23]. In this model some covariate effects work additively on the hazard function and other covariates are allowed to have multiplicative effects. Factors holding the assumption of proportionality of the hazards as the cost accumulation increases were included in the multiplicative part of the Cox-Aalen model (i.e., Cox part). These results are expressed as hazard ratios (HR) of interrupting the cost accumulation process as in a traditional Cox model.

Covariates that were expected to have effects that varied at different levels of the cost accumulation process (i.e., cost-varying) were included in the additive part of the Cox-Aalen model (i.e., Aalen part). Results are shown graphically as cumulative additive effects (with 95% point-wise confidence bands) of each covariate on the hazard of interrupting the cost accumulation process, plotted against cumulative costs at the end of follow-up. The slope of cumulative function provides information about the influence of the covariate. If the effect is constant (or cost-invariant) the plot should approximate a straight line. A cumulative function increasing above zero describes the effect of a covariate that increases the hazard of ending follow-up at lower costs with respect to the reference category. The crude probability of interrupting the cost accumulation process at the end of the follow up for the different categories of the cost-varying variables has also been depicted in the Kaplan-Meier curves. Predicted median costs from Cox-Aalen model results were estimated for some scenarios, suggested from observed data, along with 95% bootstrap CIs.

Results

In the period 2000-2005 the CCRP had 917 registered incident cases of cancer in children and adolescents. During 3 years of follow-up after cancer diagnosis, 18 (1.8%) had no recorded episodes of care, and were excluded. This group had demographic and clinical characteristics similar to the group with episodes of care, and the missing information is probably due to errors in record linkage identification codes, or changes of residence. In total, 13,433 episodes of care provided to 899 children were included in the analysis (median: 11; I-III quartile: 4-24). Table II describes the characteristics of the analysed cohort of children and adolescents (Table II).

Table III describes the episodes of care in terms of frequency and duration of treatment (in days), by several characteristics. Almost half of the episodes of care were inpatient (median duration: 4 days), while outpatient radiotherapy represented only 1.7% of all episodes of care, but with a median duration of 20 days. Treatment complexity was high for two out of three episodes of care, with a slightly longer median duration. Sixty-five percent of care was supplied at the RRC and 40% of the patients received care exclusively at the RCC during the study period. Episodes of care at hospitals outside the Piedmont Region accounted for 16% of care. There was no difference in treatment duration (median: 3 days) by type of centre, except for adult oncology centres (median: 4 days; I-III quartile: 1-9). Seventy-five percent of all treatments occurred within 1 year of cancer diagnosis, with a higher proportion of high complexity episodes of care (71% vs. 44% in the third year).

Table IV describes the variables analysed in the Cox-Aalen models, distinguishing those included in the Aalen part from those in the Cox part and, for the latter, the HRs (p-value) of interrupting the cost accumulation process. The cumulative additive effects function plotted against cumulative costs at the end of follow-up, is shown for the variables with a significant

impact (Figure 1): age at diagnosis and cancer type. For these two cost-varying covariates the crude effect is also described by the Kaplan-Meier curves (Supplemental Figure 1).

The overall median estimated economic burden of caregiving by one of the parents at the end of follow-up was €5,895 (US\$7,954), which is around 7% of the annual per person GDP in the Piedmont Region in 2008. Episodes of care delivered in hospitals/centres other than the RRC increased the hazard of interrupting the cost accumulation process, and was a rough predictors of lower cost at the end of follow-up. The economic burden of caregiving also decreased slightly throughout the period of cancer diagnosis considered (2000-2005). Older age at diagnosis reduced the probability of higher cost significantly, at least up to €5000(US\$6,746). Above this level the effect of age at diagnosis was not significant, as suggested by the lower confidence band crossing the cost axis (Figure 1a). The increasing cumulative functions shown in Figure 1 indicate that, compared to leukaemia, all the other cancer types predict a significantly smaller economic burden of caregiving on families of children and adolescents with cancer. These cumulative functions for the effect of cancer type decreased roughly after the €7,500 (US\$10,120) mark, suggesting an effect reduction.

Table V shows the estimated median economic burden for families of children/adolescents who received care at the RCC, as this was the centre most utilised among the observed patterns of care. The most relevant differences can be observed by cancer type. For leukaemia the median economic burden at 3 years was above €10,000 (US\$13,493), with narrow CIs. The cancer types with the best prognosis had a median economic burden of around €2,000 (US\$2,699) in 2005. The decreasing economic burden observed with older age at cancer diagnosis and more recent year of treatment is present, but not that relevant, as evidenced by the overlapping CIs (Table V).

In the sensitivity analysis, the median economic burden varied from €4,480 (US\$6,045) in the minimum scenario, to €9,746 (US\$13,150) in the maximum scenario. The effect of each covariate on the economic burden did not differ from the base case scenario.

Discussion

This study estimated the economic burden of caregiving on families of children and adolescents with cancer at a population level, without the direct involvement of families. Even if the crude results are likely underestimated, administrative healthcare data made it possible to describe factors associated with such costs. The identification of significant determinants of economic burden is of relevance for implementing targeted family support programmes.

The economic burden of caregiving increased when episodes of care were supplied at the RRC, and when treatment complexity was high. The association between episodes of care at the RRC and treatment complexity proves that the Regional Network for Childhood Cancer Care is following the Regional Plan for Paediatric Oncology and Haematology Care.

During the period of cancer diagnosis considered (2000-2005) the economic burden of caregiving decreased slightly. This decrease is partially due to a shift from inpatient care to day-care, together with an improvement in care management due to the regional network mentioned above.

Particular attention and support should be devoted to families of younger children, as they are exposed to a higher economic burden due to caregiving. Among the cancer types, leukaemia required a higher family commitment than any other cancer considered, which lead to a higher economic burden, an effect which was highest up to €7,500 (US\$10,120). Above that amount, the economic burden of caregiving observed for other cancer types with

a poorer prognosis slowly approached that of leukaemia. The described effect of covariates was confirmed in the minimum and maximum scenarios.

Our results are in line with the study by Limburg et al.[24] on the impact of childhood cancer on parental employment, where parents with children under 10 years of age, and parents of children diagnosed with leukaemia were most likely to leave their jobs.

The study focused on a single cost item – caregiving during episodes of care – and calculated costs from a societal point of view. A real estimate of family expenditure was not performed, as the study design was based on administrative data. Indeed, although several other factors are of interest in estimating the total economic burden of caregiving on families of children and adolescents with cancer, they are not captured in administrative data. Only direct investigation with involvement of families, by means of a retrospective questionnaire or diary, could allow a complete collection of the data of interest. Nevertheless, our usage of administrative data has avoided problems of non-response and selection bias. A review by Tsimicalis and colleagues reinforced the importance of adopting strategies for reducing bias due to selection, sampling frame and size, non-response, withdrawal and attrition [8]. The data sources used in our study have the strong advantage of covering the entire population of interest (all the incident cases during the selected period), with a standardised level of completeness of information.

In conclusion, the estimates of the economic burden of caregiving on families of children and adolescents with cancer derived from administrative data should be considered a minimum burden, but the estimated effect of the covariates is informative for healthcare decision makers in planning support programmes for families.

Figures

Fig.1. Estimates of cumulative effects (Aalen coefficients; 95% confidence intervals) on cost for caregiving at 3 years of follow-up of: increasing age at diagnosis (A) and cancer type versus leukaemia (B: Hodgkin Disease, Wilms Tumour, Retinoblastoma, Gonadic Tumour, all other tumours; C: Malignant Bone Tumours, Soft Tissue Sarcoma; D: Non-Hodgkin lymphoma, Neuroblastoma, Central Nervous System).

Supplemental Fig.1. Kaplan-Meier curve of age at diagnosis (A) and cancer type (B): rough probability of accumulating cost at the end of the follow up.

For Peer Review

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TABLE I. Three-year survival by cancer type, in a cohort of children and adolescents diagnosed with incident cancer in the Piedmont Childhood Cancer Registry, 2000-2005

Cancer type	N=899*	3-year survival	
		(%)	95% CI
Hodgkin Disease	111	96.4	93.0-1.00
Wilms Tumour	30	93.3	84.8-1.00
Retinoblastoma	12	91.7	77.3-1.00
Gonadic Tumour	50	90.0	82.1-98.7
All other tumours	84	85.7	78.5-93.5
Non-Hodgkin lymphoma	66	78.8	69.5-89.3
Central Nervous System Tumours	180	77.7	71.9-84.1
Neuroblastoma	61	75.4	65.3-87.0
Malignant Bone Tumours	44	59.1	46.2-75.6
Soft Tissue Sarcoma	61	65.4	54.0-79.1
Leukaemia	200	88.9	84.7-93.4

During 3 years of follow-up after cancer diagnosis, no episodes of care were identified for 18 children. Therefore, 899 children were included in the analysis out of 917. CI=confidence interval.

TABLE II. Characteristics of children and adolescents diagnosed with incident in the Piedmont Childhood Cancer Registry, 2000-2005

	N=899	%
Male, %	501	55.7
Age at diagnosis, years		
0	60	6.7
1-4	229	25.5
5-9	141	15.7
10-14	178	19.8
15-19	291	32.4
Cancer type		
Hodgkin Disease, Wilms Tumour, Retinoblastoma, Gonadic Tumours, All other tumours	287	31.9
Non-Hodgkin lymphoma Central Nervous System, Neuroblastoma	307	34.1
Malignant Bone Tumours, Soft Tissue Sarcoma	105	11.7
Leukaemia	200	22.2
Year of diagnosis		
2000	152	16.9
2001	141	15.7
2002	158	17.6
2003	152	16.9
2004	168	18.7
2005	128	14.2
Travel time		
Same town	162	18.0
Within 30 min	148	16.5
Within 1 h.	239	26.6
More than 1 h.	350	38.9
Vital status 3 years after diagnosis: deceased	136	15.1

RRC= Regional Referral Centre.

TABLE III. Episodes of care during 3 years of follow-up after cancer diagnosis: frequency and duration of treatment (days) (median; I-III quartile)

	N	(%)	N of patients	Duration of treatment (days) Median (I-III quartile)
Overall	13,433	-	899	3 (1-6)
Clinical setting				
Inpatient	6,808	50.7	752	4 (2-7)
Day-care	6,396	47.6	850	2 (1-4)
Outpatient radiotherapy	229	1.7	218	20 (11-31)
Type of treatment				
Transplant	210	1.6	153	25 (20-37)
Major surgery	1,155	8.6	627	6 (2-11)
Minor surgery	309	2.3	219	3 (1-7)
Radiotherapy	327	2.4	265	15 (2-25)
Chemotherapy	7,242	53.9	603	3 (2-5)
Other medical care	4,190	31.2	769	2 (1-6)
Treatment complexity				
Low	4,478	33.3	794	2 (1-6)
High	8,955	66.7	852	3 (2-6)
Type of centre				
RRC	8,712	64.9	556	3 (1-6)
Satellite Units	1,255	9.3	264	3 (1-7)
Adult oncology centres	894	6.7	231	4 (1-9)
Other hospitals in Piedmont Region	495	3.7	221	3 (1-7)
Hospitals in other regions of Italy	2,077	15.5	253	3 (1-7)
Period of treatment				
First year	10,119	75.3	895	3 (2-7)
Second year	2,238	16.7	477	2 (1-5)
Third year	1,076	8.0	323	2 (1-6)

RRC= Regional Referral Centre.

TABLE IV. Factors affecting the probability of interrupting the cost accumulation process at the end of follow-up

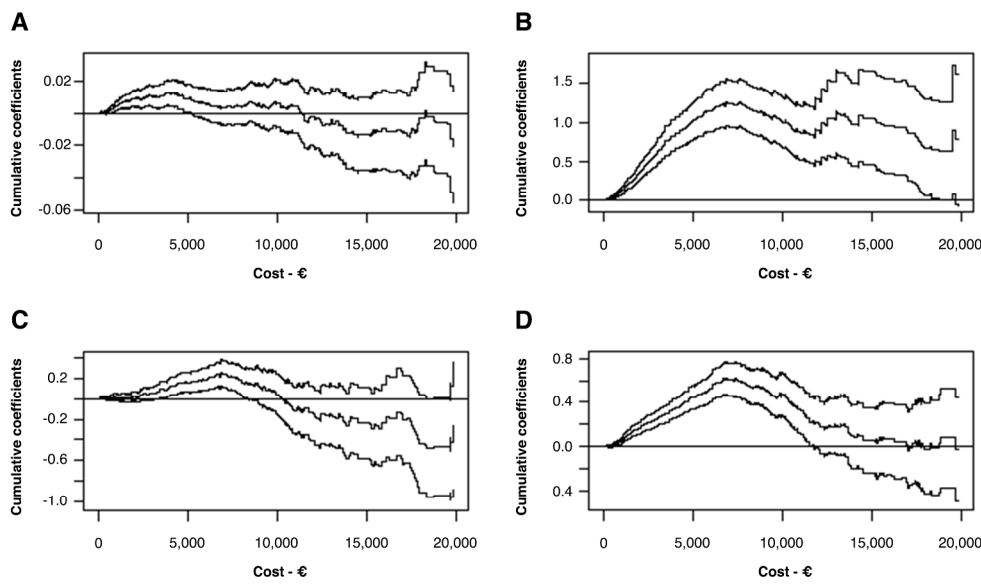
	HR	95% CI	p value
Age at diagnosis (unit increase)		<i>Additive model*</i>	
Cancer type (Leukaemia as reference)		<i>Additive model*</i>	
Year of diagnosis (unit increase)	1.067	1.02 - 1.12	0.004
Type of centre			
RRC (reference)	-	-	-
Satellite Units	1.168	0.89 - 1.53	0.259
Adult Oncology Centres	1.363	1.02 - 1.82	0.035
Other hospitals in Piedmont Region	1.530	1.05 - 2.24	0.028
Hospitals in other regions of Italy	1.231	0.98 - 1.55	0.077
Travel time		<i>Not included</i>	
Treatment complexity (low as reference)		<i>Not included</i>	

HR=hazard ratios; RRC= Regional Referral Centre; CI=confidence interval. *Variable included in the additive part of Cox-Aalen model (i.e. Aalen part) because expected to have cost-varying effects. See Figure 1 for effects.

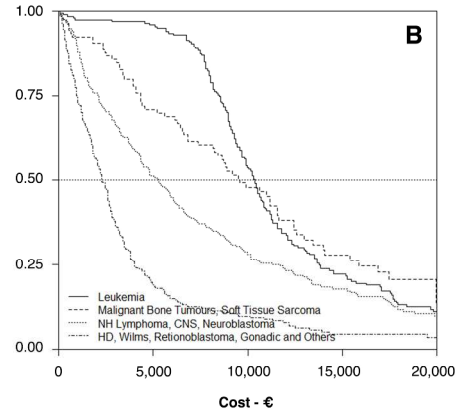
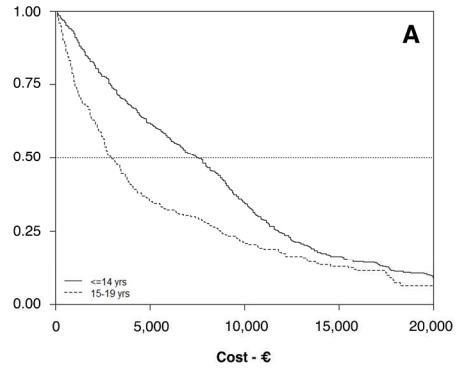
TABLE V. Estimated median economic burden (€ and US\$) of caregiving after 3-years of follow-up (bootstrapped 95% CIs), for several observed scenarios for children receiving care at the RCC

Year	Type of cancer	Age at cancer diagnosis							
		5 years				14 years			
		€	95% CI	\$	95% CI	€	95% CI	\$	95% CI
2000	Leukaemia	11,161	10,492-11,869	15,060	14,157-16,015	11,004	10,293-12,973	14,848	13,888-17,504
	Malignant Bone Tumours, Soft Tissue Sarcoma	-*	-*	-*	-*	9,196	6,309-11,240	12,408	8,513-15,166
	Non-Hodgkin lymphoma Central Nervous System, Neuroblastoma	7,664	5,893-9,006	10,340	7,951-12,152	6,838	5,256-8,725	9,227	7,092-11,773
	Hodgkin Disease, Wilms Tumour, Retinoblastoma, Gonadic Tumours, all other tumours	3,380	2,672-4,009	4,560	3,605-5,409	3,065	2,437-3,460	4,136	3,288-4,669
2005	Leukaemia	10,257	9,581-10,689	13,840	12,928-14,423	9,904	9,386-10,611	13,363	12,665-14,317
	Malignant Bone Tumours, Soft Tissue Sarcoma	-*	-*	-*	-*	9,511	8,174-12,205	12,833	11,029-16,468
	Non-Hodgkin lymphoma Central Nervous System, Neuroblastoma	5,581	4,440-6,052	7,530	5,991-8,166	4,795	3,536-5,816	6,469	4,771-7,848
	Hodgkin Disease, Wilms Tumour, Retinoblastoma, Gonadic Tumours, all other tumours	-*	-*	-*	-*	2,358	1,768-2,594	3,182	2,386-3,500

CI=confidence interval. *Not observed scenario.



237x143mm (300 x 300 DPI)



237x125mm (300 x 300 DPI)

Peer Review